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Review

Application of terahertz pulsed imaging to analyse film coating characteristics of sustained-release coated pellets

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ABSTRACT

Terahertz pulsed imaging (TPI) was employed to explore its suitability for detecting differences in the film coating thickness and drug layer uniformity of multilayered, sustained-release coated, standard size pellets (approximately 1 mm in diameter). Pellets consisting of a sugar starter core and a metoprolol succinate layer were coated with a Kollicoat® SR:Kollicoat® IR polymer blend for different times giving three groups of pellets (batches I, II and III), each with a different coating thickness according to weight gain. Ten pellets from each batch were mapped individually to evaluate the coating thickness and drug layer thickness between batches, between pellets within each batch, and across individual pellets (uniformity). From the terahertz waveform the terahertz electric field peak strength (TEFPS) was used to define a circular area (approximately 0.13 mm^2) in the TPI maps, where no signal distortion was found due to pellet curvature in the measurement set-up used. The average coating thicknesses were 46 μm, 71 μm and 114 μm, for batches I, II and III respectively, whilst no drug layer thickness difference between batches was observed. No statistically significant differences in the average coating thickness and drug layer thickness within batches (between pellets) but high thickness variability across individual pellets was observed. These results were confirmed by scanning electron microscopy (SEM). The coating thickness results correlated with the subsequent drug release behaviour. The fastest drug release was obtained from batch I with the lowest coating thickness and the slowest from batch III with the highest coating thickness. In conclusion, TPI is suitable for detailed, non-destructive evaluation of film coating and drug layer thicknesses in multilayered standard size pellets.

Contents

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1. Introduction

Multiparticulate dosage forms are desirable drug delivery systems owing to a number of advantages over single unit dosage forms, such as better control of the gastric transit time and associated drug absorption, and a lower susceptibility to dose dumping (Bechgaard and Nielsen, 1978). Frequently, the particles are coated to modify drug release kinetics. Thus, the product performance directly correlates with critical film coating quality attributes, including the coating thickness and uniformity (Haddish-Berhane et al., 2006).

Routinely, indirect monitoring methods such as the product weight-gain and the amount of coating polymer applied are used to infer the pellet film coating thickness (and thus the coating quality) (Ringqvist et al., 2003). For complex systems, e.g. drug-layered sugar starter cores coated with a sustained-release coating, the non-specific character of the weight-gain measurements as well as the fact that coating thickness uniformity can be related to the drug layer surface morphology, render weight-gain as a sole indication of the coating quality insufficient (Ho et al., 2008, 2010). Thus, a number of studies using mechanical analysis, e.g. in vitro drug release testing, have been used to obtain more insight into pellet coating structures and their effects on drug release (Siepmann et al., 2007, 2008; Muschert et al., 2009). Those mechanistic methods provide deeper understanding of the drug release mechanism from the coated dosage form, but prove largely unsuitable to provide detailed information on critical film coating quality attributes such as coating thickness, uniformity and morphology. Information on the coating thickness, uniformity and morphology may be obtained with other analytical techniques including scanning electron microscopy (SEM)(Heinicke and Schwartz, 2007), fluorescence microscopy (Andersson et al., 2000), atomic force microscopy (AFM)(Ringqvist et al., 2003), confocal Raman microimaging (Ringqvist et al., 2003), energy dispersive X-ray imaging (EDX)(Ensslin et al., 2008), nuclear magnetic resonance spectroscopy (NMR)(Ensslin et al., 2008), electron paramagnetic resonance spectroscopy (EPR) (Ensslin et al., 2009) and confocal laser scanning microscopy (CLSM) (Depypere et al., 2009). However, the applicability of some of those characterisation methods, e.g. SEM, fluorescence microscopy, atomic force microscopy and confocal Raman microimaging, is restricted to the coating surface of the sample, or the methods, e.g. SEM, fluorescence microscopy and EDX, require the samples to be cut to determine coating thickness information,, which leads to the irreversible destruction of the sample. Moreover, in NMR and EPR spectroscopy information on critical coating quality attributes can only be determined indirectly, i.e. signals are obtained during drug release testing, and CLSM needs the aid of chemometric models to evaluate coating quality characteristics.

A recently established non-destructive technique to gain deeper understanding on film coating characteristics (including coating thickness and uniformity) is terahertz pulsed imaging (TPI) (Ho et al., 2007, 2009, 2010). Terahertz radiation is part of the far infrared region of the electromagnetic spectrum (2 cm^{-1} and 120 cm^{-1}) and most of the well-established polymer formulations used in film coatings are transparent or semitransparent to the pulsed coherent light used in TPI (Zeitler et al., 2007b). Hence, the generated terahertz pulse can propagate through the sample and reflections caused by interfaces within the sample structure, due to refractive index changes, can be measured against time. Thus, single or multiple layer thicknesses (at depth) can be derived from the peak-to-peak distance in the time-domain signal (time delay of the terahertz pulse) (Fitzgerald et al., 2005). Importantly, not only the average coating thickness, but also the critical coating quality attribute coating uniformity, can be accessed by TPI. Coating uniformity has been shown to affect drug release behaviour from coated dosage forms (Ho et al., 2008, 2010). Although most analyses of film coatings using TPI have involved tablets, recently, TPI has also been shown suitable for the analysis of coating and internal drug layer thicknesses and uniformities in large sustained-release coated pellets (6 mm in diameter) (Ho et al., 2010).

In this study, TPI was employed for the first time to analyse film coating and internal drug layer thicknesses and uniformity in standard size pellets (1 mm in diameter). Furthermore, the effect of coating characteristics on the subsequent drug release behaviour of the pellets was investigated.

2. Materials and methods

2.1. Materials

The following materials were used: metoprolol succinate (Salutas Pharma GMBH, Germany); nonpareil sugar starter cores (diameter 710–850 μm, NP Pharma SR, France); polyvinyl acetate (Kollicoat SR 30 D; BASF, Germany), poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (Kollicoat IR; BASF, Germany); hydroxypropyl methylcellulose (HPMC, Methocel E5; Colorcon, United Kingdom); triethyl citrate (TEC; Morflex, USA); and talc (Luzenca Val Chisone, Italy).

2.2. Preparation of the pellets

Pellets were prepared by layering an aqueous drug-binder solution (20% metoprolol succinate, 1% HPMC) onto sugar starter cores (diameter = 710–850 μm; Boire, France) until a 10% (w/w) drug load using a fluidized bed coater equipped with a Wurster insert (Strea 1; Aeromatic-Fielder, Switzerland). A spray rate of 2–3 g/min, a spray nozzle of 1.2 mm diameter and an atomisation pressure of 1.2 bar was used to apply the drug-binder solution. The inlet temperature was 40 ± 2 °C and the product temperature 38 ± 2 °C. The method used to apply the drug layer onto the sugar starter cores resulted in a visually smooth surface.

Kollicoat® IR (polyvinyl alcohol–polyethylene glycol graft copolymer) was dissolved in purified water and blended with plasticised Kollicoat® SR 30 D (an aqueous polyvinyl acetate dispersion) (overnight stirring with 5% triethyl citrate, w/w based on the polymer content) 30 min prior to the coating process. The polymer:polymer blend ratio was 25:75 (w/w referring to the dry mass). Talcum (1.5%) was added (w/w; based on the total solids content) and the dispersion was gently stirred throughout the coating process. The process parameters were as follows: inlet temperature 38 ± 2 °C, product temperature 35 ± 2 °C, spray rate 2–3 g/min, atomisation pressure 1.2 bar, nozzle diameter 1.2 mm. After coating, the pellets were further fluidised for 10 min and subsequently cured in an oven for 24 h at 60 °C. The metoprolol succinate loaded cores were coated until a coating thickness of approximately 40, 60 and 100 μm (estimated based on weight-gain) was achieved. The overall minimum, maximum and the average diameter (measured in *x* and *y* directions for each pellet) from 10 pellets of each batch were determined using an electronic calliper (TESA Technology, Switzerland). The results were as follows: 830 μm, 1250 μm and 969 (±95) μm for batch I; 940 μm, 1160 μm and 1043 (±58) μm for batch II; and 990 μm, 1390 μm and 1144 (±104) μm for batch III.

2.3. Terahertz pulsed imaging (TPI)

A total of ten pellets in each batch were imaged individually using a TPS Spectra3000 (TeraView Ltd., Cambridge, UK) in reflection mode. The single pellets were fixed on a glass slide and the terahertz incident beam was manually focussed on the highest point of the pellet surface by moving the *x*–*y* stage. The instrument set-up involved mapping a 1.2 mm × 1.2 mm area with a step-size